Effects of Continuous Positive Airway Pressure Therapy in Three Japanese Patients with Obstructive Sleep Apnea and Resistant Hypertension

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Abstract

The following three case reports present the effects of 6-month continuous positive airway pressure (CPAP) therapy on blood pressure (BP) in severe obstructive sleep apnea patients with resistant hypertension.

Case 1 A 58-year-old woman exhibited a decreased 24-hour BP and changes in the nocturnal BP dipping pattern from non-dipper to dipper. **Case 2** A 64-year-old man showed no improvements in nocturnal BP.

Case 3 A 78-year-old man with ischemic cardiomyopathy exhibited changes in the nocturnal BP dipping pattern from non-dipper to dipper. These results suggest that 6-month CPAP therapy improves the nocturnal BP dipping status in some patients with obstructive sleep apnea and resistant hypertension.

Key words: polysomnography, ambulatory blood pressure monitoring, sleep-disordered breathing, positive airway pressure, circadian rhythm

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Introduction

The mechanisms of obstructive sleep apnea (OSA) are closely associated with the development of hypertension. The incidence of resistant hypertension is particularly high in OSA patients, in spite of the use of three or more antihypertensive agents from different classes (1). Continuous positive airway pressure (CPAP) therapy also exerts hypotensive effects on OSA patients with resistant hypertension. The effects of CPAP therapy in Westerners have been reported (2, 3); however, only a handful of case reports of Japanese patients have been published. We herein report the hypotensive effects of CPAP therapy in Japanese OSA patients with resistant hypertension.

Case Reports

Materials and methods

This case report includes the cases of three Japanese patients with resistant hypertension who exhibited uncontrolled

blood pressure (BP; clinic BP $\geq 140/90$ mmHg) despite receiving treatment with three or four antihypertensive drugs. All risk factors for secondary hypertension, except for OSA, were ruled out based on the findings of ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT) and blood sampling. The presence of OSA was determined using full polysomnography (PSG) with the SLEEP WATCHER[®] (Compedics, Australia). Clinic BP was measured twice in our outpatient facility between 09:00 and 17:00 according to the cuff-oscillometric method using an electronic arm cuff device in the sitting position after 3-5 minutes of rest. Noninvasive ambulatory BP monitoring (ABPM) was performed for 24 hours using an FM-800[®] [Fukuda Denshi Ltd., Tokyo, Japan (4)] at 30-minute intervals before and after six months of CPAP therapy (5). The average duration of CPAP use was calculated using a memory card embedded in the CPAP machines. The ABPM data were analyzed based on the method described by Kario et al. [Fig. 1 (6)]. Each patient recorded when they fell asleep at night and woke in the morning on the ABPM. The study protocol was approved by the St. Marianna University School of Medicine Institutional Committee on Human Re-

Hypertension: $\geq$ 24-hour blood pressure 130/80 mmHg		
Normal blood pressure: < 24-hour blood pressure 130/80 mmHg		
Nocturnal hypertension: $\geq$ nocturnal blood pressure 120/70 mmHg		
Nocturnal blood pressure dipping patterns		
Dippers:	$100 \times (1 - \text{sleep SBP} / \text{awake SBP}) \geq 10\%$	but < 20%
Non-dippers:	//	$\geq 0\%$ but < 10%
Risers:	//	< 0%
Extreme dippers:	//	$\geq 20\%$

SBP: systolic blood pressure

Figure 1. Circadian blood pressure changes. The circadian blood pressure was assessed using ambulatory blood pressure monitoring (ABPM) (6). SBP: systolic blood pressure

search. Informed consent was obtained from all patients prior to enrollment.

Case 1

A 58-year-old woman had a history of snoring for several years. In 2010, she presented to our hospital with suspected OSA, a contributing factor for resistant hypertension. Upon hospital arrival, her height was 154 cm, her body weight was 61.0 kg and her body mass index (BMI) was 25.7 kg/m². Her previous medical history included the use of antihypertensive therapy since 2008 (olmesartan: 40 mg, amlodipine: 5 mg, trichlormethiazide: 2 mg) and reflux esophagitis with no alcohol intake or smoking habits. The results of 24-hour ABPM suggested that the patient had hypertension (24-hour BP, 131.8/84.2 mmHg), nocturnal hypertension and a non-dipper status with a 6% night-time BP decline (Table 1, Fig. 2). The Epworth sleepiness score (ESS) was 4 points. The patient's sleep study data are shown in Table 2. She was diagnosed with severe OSA, and CPAP therapy was initiated following the titration of pressure limits of 4 to 10 cm H₂O (Table 2). The average duration of CPAP use was 6.5 hours/night, and the patient experienced no changes in prescribed medications during the treatment period. After six months of CPAP therapy, the ESS was 4 points, the patient's BMI was 26.1 kg/m² and ABPM revealed a normal BP, nocturnal hypertension and an improved nocturnal BP dipping pattern from a non-dipper (6%) to a dipper (11%) status (Table 1, Fig. 2).

Case 2

A 64-year-old man was diagnosed with hypertension in 2005. Upon hospital arrival, his height was 161 cm, his body weight was 66.9 kg and his BMI was 25.8 kg/m². He was an opportunity drinker and had given up smoking 10 years earlier. The prescribed medications included telmisartan (80 mg), azelnidipine (16 mg), carvedilol (10 mg) and trichlormethiazide (2 mg). The results of 24-hour ABPM suggested that the patient had hypertension (24-hour BP, 146.1/79.5 mmHg), nocturnal hypertension and a non-dipper status with a night-time BP decline of only 3% (Table 1, Fig. 2). The ESS was 8 points. The results of PSG are shown in Table 2. CPAP titration was performed to obtain a detailed evaluation. CPAP therapy was subsequently initiated

following titration of the lower and upper pressures to 4 and 12 cm H₂O, respectively. The patient experienced no changes in prescribed medications throughout the treatment period. After six-months of CPAP therapy, the patient lost 0.4 kg in weight and his BMI was 25.7 kg/m², the average duration of CPAP use was 4.0 hours/night, the ESS was 4 points and ABPM showed nocturnal hypertension and a non-dipper pattern with a 5% night-time BP decline (Table 1, Fig. 2).

Case 3

A 78-year-old man was admitted to our hospital with dyspnea and pitting edema of the lower extremities in 2010. He was diagnosed with congestive heart failure due to ischemic cardiomyopathy and an old antero-septal myocardial infarction. His medical history included a prior acute myocardial infarction, hypertension and dyslipidemia diagnosed 10 years earlier. Since frequent snoring and apnea were evident during admission, he was suspected to have OSA and underwent ABPM and PSG two months after discharge. His height was 157 cm, his body weight was 62.1 kg and his BMI was 25.2 kg/m². He did not drink alcohol or smoke cigarettes. His medications included candesartan (8 mg), carvedilol (10 mg) and furosemide (20 mg). Transthoracic echocardiography showed decreased left ventricular wall motion and thickening in the anterior and septal walls of the left ventricle. The Simpson's left ventricular ejection fraction was 32%. The left ventricular end-diastolic and end-systolic dimensions were 64 mm and 54 mm, respectively. Color Doppler echocardiography showed no significant valvular heart disease. The ratio of the early diastolic mitral flow velocity to the early diastolic mitral annular velocity was 12.0. The laboratory data showed a hemoglobin level of 9.7 g/dL, a creatinine level of 0.95 mg/dL, a blood urea nitrogen level of 14.0 mg/dL and a brain natriuretic peptide level of 125.4 pg/mL. The results of 24-hour ABPM suggested that the patient had hypertension (24-hour BP, 142.9/79.7 mmHg), nocturnal hypertension and a non-dipper status with an 8% night-time BP decline (Table 1, Fig. 2). The ESS was 0 points. Table 2 shows the results of PSG. The patient received CPAP therapy following titration of the pressure limits at 4 to 12 cm H₂O. The average duration of CPAP use was 5.6 h/night, and the patient experienced no prescribed medication changes during the treatment period. After six-months of CPAP therapy, the patient's BMI was 25.1 kg/m² and ABPM showed nocturnal hypertension and a dipper pattern with a decreased night-time BP (14%; Table 1 and Fig. 2).

Discussions

OSA is readily diagnosed and usually treatable, although it is a risk factor for resistant hypertension, which is often uncontrollable, even with the use of three or more antihypertensive agents (1). Kario (7) recommended the use of CPAP therapy in OSA patients with an AHI of ≥ 20 /hour

Table 1. Changes in Blood Pressure before and after Six-months of Continuous Positive Airway Pressure Therapy

	Period	Clinic BP (mmHg)	24-hour BP (mmHg)	Diurnal BP (mmHg)	Nocturnal BP (mmHg)	Dipping status (%)
Case 1	Baseline	157 / 96	131.8 / 84.2	134.7 / 87.4	127.1 / 79.1	6
	6 months	132 / 88	121.8 / 78.6	125.9 / 80.2	112.4 / 75.1	11
Case 2	Baseline	148 / 72	146.1 / 79.5	148.5 / 81.3	135.9 / 71.9	3
	6 months	134 / 60	148.8 / 76.8	157.0 / 83.4	134.4 / 65.2	5
Case 3	Baseline	161 / 93	142.9 / 79.7	144.6 / 82.9	140.4 / 74.9	8
	6 months	126 / 72	137.8 / 70.9	140.9 / 72.4	133.7 / 69.0	14

BP: blood pressure

Figure 2. Blood pressure before and after six-months of continuous positive airway pressure therapy. The patients' blood pressure was measured at 30-minute intervals using ABPM. This figure presents the blood pressure values obtained at 1-hour intervals using ABPM. Decreases in 24-hour blood pressure, diurnal blood pressure and nocturnal blood pressure were observed in Cases 1 and 3. In addition, the dipping status improved in Cases 1 and 3.

complicated by hypertension. Bazzano et al. (2) reviewed 255 reports of 16 randomized clinical trials and concluded that 2-week CPAP therapy decreases the BP values in OSA patients. Akashiba et al. (8) reported that 3-day CPAP therapy reduces diurnal and nocturnal BP and results in changes from a "non-dipper" to a "dipper" status in OSA patients. Lozano et al. (3) demonstrated that, in their study, 3-month CPAP treatment achieved reductions in 24-hour systolic BP (-9.71 mmHg), 24-hour diastolic BP (-6.98 mmHg), and daytime diastolic BP (-6.12 mmHg) in OSA patients with ABPM-confirmed resistant hypertension. These results were obtained from small- to large-scale studies (2, 3, 8); therefore, the hypotensive effects of CPAP therapy may vary among patients with different backgrounds. In addition, most earlier studies of OSA were conducted in the West and included relatively obese patients. It thus remains uncertain

whether the results of these studies are applicable to non-obese Japanese patients with OSA.

Of our patients with resistant hypertension, two (Cases 1 and 3) exhibited improvements in the nocturnal BP dipping status after six-months of CPAP therapy and one (Case 2) did not. Heart failure patients with a reduced ejection fraction, as observed in Case 3, tend to exhibit a non-dipper pattern (9), although, in both Cases 1 and 3, the nocturnal BP dipping pattern changed from a non-dipper to a dipper status following the administration of CPAP therapy. A non-dipper status is associated with the prognosis of end-organ damage (6, 10). In our cases, particularly Case 2, no significant decreases in BP were observed. This finding was presumed to be due to the patients' older age (11), lower BMI compared with that of study patients evaluated in published reports in Europe and the United States (2, 12) and short

Table 2. Sleep Study Data

	Period	AHI (/h)	AI (/h)	CA (/h)	OA (/h)	MA (/h)	Arousal index (/h)	Sleep stage 3+4 (%)	REM sleep (%)	lowest oxygen saturation (%)
Case 1	Baseline	38.1	11.6	0.3	11.2	0.1	32.1	6.5	11.9	79
	After CPAP titration	4.9	0.4	0.4	0.0	0.0	22.5	36.0	15.7	93
Case 2	Baseline	51.2	47.0	2.3	44.3	0.4	62.0	0.0	9.2	80
	After CPAP titration	1.5	1.0	0.2	0.8	0.0	23.6	9.8	15.8	94
Case 3	Baseline	90.4	76.5	3.8	69.8	2.9	103.9	0.0	13.8	76
	After CPAP titration	3.8	0.5	0.3	0.2	0.0	17.5	11.3	19.7	90

AHI: apnea-hypopnea index, AI: apnea index, CA: central apnea, OA: obstructive apnea, MA: mixed apnea, REM: rapid eye movement, CPAP: continuous positive airway pressure

duration of CPAP use (2). Meanwhile, intermittent hypoxia in patients with OSA influences the progression of cardiovascular disorders (13, 14). The hypotensive effects of CPAP therapy on OSA associated with resistant hypertension were insufficient in our patients, although CPAP therapy does improve hypoxia, which results in a better prognosis of OSA. Accordingly, the outcomes of our patients suggest that CPAP therapy is likely associated with a better long-term prognosis and that its effects differ in OSA patients with resistant hypertension with different backgrounds.

We herein presented the cases of three severe OSA Japanese patients with resistant hypertension who were treated with CPAP therapy, which resulted in improvements in the dipping status and prognosis. Further data accumulation with larger study populations is required to verify the effects of CPAP therapy.

The authors state that they have no Conflict of Interest (COI).

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